Longitudinal changes in vascular function parameters in pregnant women with chronic hypertension and association with adverse outcome: a cohort study

Article

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Longitudinal changes in vascular function parameters in pregnant women with chronic hypertension and association with adverse outcome: a cohort study

Short Title: Maternal haemodynamics and pregnancy outcome

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ABSTRACT

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Objectives

Raised vascular function measures are associated with development of adverse maternal and perinatal outcomes in low risk pregnancy. This study aimed to evaluate the association between longitudinal vascular function parameters and adverse outcomes in pregnant women with chronic hypertension.

Methods

Pregnant women recruited to the PANDA (Pregnancy And chronic hypertension: NifeDipine vs lAbetalol as antihypertensive treatment) trial in three UK maternity units had serial pulse wave analyses performed using the Arteriograph® (Tensiomed, Budapest, Hungary) while in a sitting position from 12 weeks onwards. Statistical analysis used random-effects logistic regression models and compared those who developed superimposed pre-eclampsia (SPE) to those who did not, women who delivered a small for gestational age infant (<10th birthweight centile) (SGA10) to those who delivered an infant with birthweight >10th centile, and women of Black ethnicity with women of non-Black ethnicity.

Results

The cohort included 97 women (90% (n=87) randomised to antihypertensive treatment), with up to six longitudinal vascular function assessments (mean 3), (57% (n=55) of Black ethnicity) with chronic hypertension and singleton pregnancies. SPE was diagnosed in 18% (n=17) and 30% (n=29) of infants were SGA10. In women who developed subsequent SPE compared to those who did not, mean brachial systolic blood pressure (SBP) (148 vs 139 mmHg; p=0.002), mean diastolic blood pressure (DBP) (87 vs 82 mmHg; p=0.01), mean central aortic pressure (139 vs 128 mmHg; p=0.001) and mean augmentation index (AIX-75) (29 vs 22%; p=0.01) were significantly higher across gestation. Mean brachial SBP (146 vs 138 mmHg; p=0.001), mean DBP (86 vs 82 mmHg; p=0.01), mean central aortic pressure (137 vs 127 mmHg; p=<0.0001), and mean PWV (9.1 vs 8.5 m/s; p=0.02) were higher across gestation in women who delivered an SGA10 infant compared to women who delivered an infant with birthweight >10th centile.

No longitudinal differences were found in the vascular function parameters in women of Black ethnicity compared to non-Black ethnicity.

Conclusion

There are persistent differences in vascular function parameters and brachial blood pressure through pregnancy in women with chronic hypertension who later develop adverse maternal and perinatal outcome. Further investigation of the possible clinical use of these findings is warranted.

INTRODUCTION

Chronic hypertension complicates 3% of pregnancies.(1, 2) The risk of adverse maternal and perinatal outcomes in women with chronic hypertension, such as SPE(3-5) and fetal growth restriction(3, 6), are dramatically increased compared to the general pregnant population. The increased maternal vascular resistance and decreased vascular compliance associated with chronic hypertension may cause maladaptation to the physiological demands of pregnancy.(7, 8) However the mechanisms underpinning these differences in pregnancy outcome in women with chronic hypertension are poorly understood.

Pulse wave analysis is a non-invasive technique that utilises the peripheral pressure waveforms, and generation of the corresponding central waveform, to derive vascular function measures of pulse wave velocity (PWV), augmentation and aortic ('central') pressure. These parameters all have prognostic value because, in the non-pregnant population, they predict increased risk of cardiovascular disease.(9-11) There is also evidence that these measures may change in pregnancy prior to development of pre-eclampsia.(12, 13) Increased brachial blood pressure is associated with subsequent adverse perinatal outcome. Previous studies have demonstrated an association between the diagnosis of pre-eclampsia and subsequent increased risk of cardiovascular morbidity and mortality.(14, 15) Investigation of arterial stiffness parameters in women with chronic hypertension in pregnancy may offer some insight into the mechanism behind this increased risk.

An association between Black ethnicity and adverse pregnancy outcome has been demonstrated.(16-19) Prevalence of chronic hypertension is higher at a younger age among Black women, compared to White,(20, 21) and Black ethnicity, compared to White, is associated with an increased lifetime risk of cardiovascular morbidity and mortality.(22, 23) A sub-analysis of the women with chronic hypertension who participated in the Vitamin In

Pregnancy trial demonstrated an association between Black ethnicity (compared to White) and SPE.(5) Exploration of the impact of ethnicity on pulse wave analyses in pregnancy complicated by chronic hypertension may provide insight into pathophysiological mechanisms underpinning ethnic differences in pregnancy outcome. This study aimed to investigate longitudinal vascular function in women with chronic hypertension in pregnancy, using pulse wave analysis, to determine if there is variation in these measures in women with subsequent SPE, SGA10 and whether these vary by baseline parameters such as Black ethnicity.

METHODS

This was a nested cohort study of women with chronic hypertension who participated in the PANDA (Pregnancy And chronic hypertension: NifeDipine vs lAbetalol as antihypertensive treatment) study between 2014 and 2016. The PANDA study was primarily a randomised controlled feasibility study comparing labetalol and nifedipine for control of chronic hypertension in pregnancy (demonstrating comparable effectiveness of both agents at controlling blood pressure to treatment target across gestation within the limitations of small numbers for this clinical endpoint). Women within the PANDA study together with those who were ineligible for randomisation (due to medication contraindication) or who declined randomisation (but met eligibility criteria) were invited to participate in this observational arm of the study. The study was registered with ISRCTN (DOI 10.1186/ISRCTN40973936, www.isrctn.com) and approved by the UK Research Ethics Committee (REC number 13/EE/0390). The study has been reported in line with STROBE guidance for reporting of cohort studies.(24)

Study Design

Women were enrolled at three consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, and St George's University Hospitals NHS Foundation Trust). The eligibility criteria included women with a prenatal diagnosis of chronic hypertension (requiring antihypertensive treatment) or blood pressure readings ≥140/90 mmHg prior to 20 weeks' gestation requiring antihypertensive treatment, as defined by the International Society for the Study of Hypertension in Pregnancy classification of hypertensive disorders of pregnancy,(25) between 12 and 27.9 weeks' gestation, singleton pregnancies, aged over 18 years, and with ability to provide informed consent. Longitudinal vascular function of the study participants was measured using pulse wave analysis. Baseline demographic and antenatal booking data were collected at enrolment. Ethnicity (Black vs non-Black) was determined by whether the woman had a parent or grandparent who was African or Caribbean by self-report. Clinical blood pressure readings taken at all subsequent antenatal visits (using automated and manual blood pressure devices) and daily during hospital admissions (highest of that day) were recorded in addition to other maternal and perinatal outcome data (SPE, mode of delivery, gestation at delivery, pregnancy loss, birthweight, birthweight centile and neonatal unit admission). SPE was defined as new-onset proteinuria, a sudden increase in proteinuria if already present in early gestation, and an increase in hypertension, as recommended by the American College of Obstetrics and Gynaecology practice bulletin.(26) Customised birthweight centiles were calculated using the GROW formula with adjustment for maternal height, maternal weight, maternal ethnicity, parity, infant sex, infant birthweight and gestation at birth (version 6.7.5.1 (2014)).(27) Infant birthweight below the 10th centile was considered diagnostic of small for gestational age (SGA10).

Pulse Wave Analysis

Pulse wave analyses were obtained using the Arteriograph® (Tensiomed, Budapest, Hungary), an oscillometric single-cuff device. Readings were obtained at study enrolment, 20 weeks, 28 weeks, and 34 weeks' gestation (+/- two weeks). All pulse wave measurements were performed with participants in the sitting position. The Arteriograph® cuff was applied to the left arm over the brachial artery for estimation of central aortic pressure (mmHg), PWV (m/s) and AIX (%). The AIX was also converted to an additional vascular function parameter AIX-75, adjusting for a heart rate of 75 beats per minute using the formula AIX -(0.431 x (75-heart rate)), in view of the linear relationship between the AIX and heart rate. The device additionally recorded brachial SBP and DBP (mmHg). All recordings were made by researchers who had received appropriate training on the use of the Arteriograph®. The results of the pulse wave analyses were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Statistical Analysis

The statistical software Stata version 14 (StataCorp, College Station, Texas) and GraphPad Prism 7 (Graph Pad Software, San Diego, California) were used for all analyses. The investigation concentrated comparison using three groupings of study women, all of whom had chronic hypertension. Grouping A: women who developed SPE compared with women who did not develop SPE. Grouping B: women who gave birth to an SGA10 infant compared with women who gave birth to an infant with a birthweight >10th centile. Grouping C: Black women compared with non-Black women. Baseline characteristics, clinical outcomes and longitudinal vascular function parameters were compared using groupings A, B, and C. Clinical brachial blood pressure measurements were also compared for each grouping.

Baseline characteristics and clinical outcomes were compared between groupings using t-tests or Mann-Whitney test for continuous variables depending on the distributions and Fisher's exact test or Chi-squared test for categorical variables. Following confirmation of Normal distribution, the mean and standard deviation (SD) of each vascular function measure within each comparison was calculated. The adjusted mean difference (AMD) and associated 95% confidence interval (CI) for each vascular function parameter was assessed for each grouping (A, B and C) using mixed effects maximum likelihood regression models allowing for gestation effects, and repeated measures in the same woman across gestation. Descriptive analysis demonstrating the variation in each vascular function parameter over gestation was conducted by calculating mean and standard error of the readings taken within 4-weekly gestation intervals (12 to 15+6, 16 to 19+6, 20 to 23+6, 24 to 27+6, 28 to 31+6 and 32 to 35+6 weeks) for each comparison adjusting for repeat readings in the same woman and displayed graphically.

RESULTS

The total number of women enrolled into this cohort study was 106 (Figure 1 details flow of study participants). Of these, four (3.8%) withdrew or were lost to follow-up, and five (4.7%) were excluded from this analysis as they had a second trimester pregnancy loss. Longitudinal vascular function assessments (290 in total) were obtained in 97 women (92%). Of the 290 readings obtained, 16 (5.5%) did not provide an AIX or PWV value and eight (2.9%) of the readings with AIX and PWV could not be included in the analyses of these parameters, as the standard deviation of the pulse wave was greater than the pre-specified 1.5 cut-off. For analysis A the cohort was divided into women diagnosed with SPE (n=17) and compared with women who were not diagnosed with SPE (n=80), for analysis B women with infants born below the 10th birthweight centile (n=29; of which n=12 also had SPE (41%)) were compared with women with infants born above the 10th birthweight centile (n=68; of which n=5 had SPE

(7.4%)), and for analysis C the cohort was divided into women of Black ethnicity (n=55) versus women self-identifying as of non-Black ethnicity (n=42). The results are presented with summary tables for comparisons of the vascular function variables within each of the three analyses (Tables 4, 5 and 6), but the figures are collated by vascular function variable across the three analyses (A, B and C) to allow visual comparison of the longitudinal variation and inter-relationship between analyses (Figures 2 to 7).

The baseline demographics of the cohort are detailed in Table 1 (and Supplementary Table S1). Body mass index was higher in the Black women compared to the non-Black women (32 kg/m^2 versus 29 kg/m^2; p=0.02). There was a lower proportion of nulliparous women in those of Black ethnicity compared to non-Black ethnicity (3.6% versus 31%; p=<0.0001), and the median antenatal booking SBP was higher in the women of Black ethnicity compared to the women of non-Black ethnicity (140 mmHg versus 134 mmHg; p=0.02). Otherwise baseline characteristics were comparable between subgroups.

Adverse maternal and perinatal outcomes were common in the cohort as a whole, with 18% (n=17) of women developing SPE in their pregnancy, 63% (n=61) of women requiring a Caesarean birth, 24% (n=23) of births occurring before 37 weeks' gestation, and 3.1% (n=3) stillbirths. Other adverse neonatal outcomes included 30% (n=29) SGA10, 14% (n=14) of infants with birthweight <3rd centile, and 22% (n=21) of infants requiring admission to the neonatal unit. There were no significant differences in maternal and perinatal outcomes between the women of Black ethnicity and non-Black ethnicity (Table 2,3, Supplementary Table S2 and S3).

The women who developed SPE had higher peak SBP and DBP (180 mmHg versus 160 mmHg; p=0.0003 and 107 versus 97 mmHg; p=0.004 respectively) and were more likely to require an

emergency Caesarean section for delivery (76% versus 39%; p=0.006) compared to those who did not. Women with SPE were delivered earlier (median 33 weeks' gestation) compared to those without (median 39 weeks' gestation; p=<0.0001) with lower birthweight babies (1560g vs. 3030g;) p=<0.0001) and with a greater proportion of infants who required admission to the neonatal unit (76% versus 10%; p=<0.0001). Similarly, amongst those who gave birth to an SGA10 infant, compared to those who gave birth to infants of birthweight >10th centile, the peak SBP and DBP were higher (175 mmHg versus 158 mmHg; p=0.001 and 100 mmHg versus 97 mmHg; p=0.048). Infants with a birthweight below the 10th centile, compared to those above, were more likely to be born before 37 weeks' gestation (52% versus 12%; p=<0.0001) and were more likely to require neonatal unit admission (48% versus 10%; p=<0.0001).

Analysis A: Comparison of vascular function parameters between women with chronic hypertension who did and did not develop superimposed pre-eclampsia

A summary of the comparison of vascular function parameters in women who did and did not develop SPE is in Table 4. Across gestation the SBP and DBP measurements taken by the Arteriograph® were higher in the women whose pregnancies were complicated by SPE (148 mmHg versus 139 mmHg; AMD 10 mmHg, 95% CI 4 to 16; p=0.002 and 87 mmHg versus 82 mmHg; AMD 5 mmHg, 95% CI 1 to 9; p=0.01), as were the central aortic pressure and the AIX adjusted for a heart rate of 75 beats per minute (139 mmHg versus 128 mmHg; AMD 12 mmHg, 95% CI 5 to 20; p=0.001 and 29% versus 22%; AMD 6 mmHg, 95% CI 1 to 11; p=0.01 respectively).

Analysis B: Comparison of vascular function parameters between women with chronic hypertension who delivered a small for gestational age infant (birthweight <10th centile) and those who delivered an infant with a birthweight ≥10th centile.

A summary of the comparison of vascular function parameters in women who gave birth to an SGA10 infant with those who gave birth to an infant with a birthweight above the 10th centile is presented in Table 5. Brachial SBP and DBP were significantly higher across gestation in the women who delivered an SGA10 infant (146 mmHg versus 138 mmHg; AMD 9 mmHg, 95% CI 4 to 14; p=0.001 and 86 mmHg versus 82 mmHg; AMD 4 mmHg, 95% CI 1 to 8; p=0.01 respectively). Mean central aortic pressure across gestation was 137 mmHg in women who gave birth to an SGA10 infant compared to 127 mmHg in women whose infant's birthweight was ≥10th centile (AMD 11 mmHg, 95% CI 5 to 18; p=<0.0001). In addition, the mean PWV across gestation was 9.1 m/s in women who delivered an SGA10 infant compared to 8.5 m/s in those who did not (AMD 0.7 m/s, 95% CI 0.1 to 1.4, p=0.02).

Analysis C: Comparison of vascular function parameters between women with chronic hypertension of Black ethnicity and non-Black ethnicity

Table 6 summarises the vascular function comparisons made between women of Black and non-Black ethnicity with chronic hypertension in pregnancy. No significant differences in vascular function across gestation were found by ethnic group.

Longitudinal variation in vascular function parameters across gestation

The graphs in Figures 2 to 7 demonstrate the gestational variation in each vascular function parameter for each comparison (A, B and C).

Comparison of clinical systolic and diastolic blood pressure readings for each comparison

Given the relationship observed between brachial SBP and DBP and outcomes as measured using the Arteriograph®, further comparison was made repeating analysis A, B and C utilising the clinically recorded blood pressure measurements taken within the study. This analysis confirmed that there was a significant relationship between brachial blood pressure and

subsequent SPE with systolic blood pressure 11 mmHg higher across gestation (95% confidence interval 7 to 15 mmHg; p <0.0001) and diastolic blood pressure 5 mmHg higher across gestation (95% confidence interval 2 to 8 mmHg; p=0.003) in women who developed SPE compared to those who did not. Raised brachial blood pressure was also associated with subsequent SGA10 in women with chronic hypertension, with systolic blood pressure 9 mmHg higher (95% confidence interval 5 to 12 mmHg; p <0.0001) and diastolic blood pressure 4 mmHg higher (95% confidence interval 1 to 6 mmHg; p 0.002) in women who gave birth to SGA10 infants compared to women who gave birth to infants who had a birthweight ≥10th centile. No relationship was demonstrated between clinical blood pressure and ethnicity. Figures 8 and 9 present the comparisons made of clinical systolic and diastolic blood pressure measurements across gestation respectively.

DISCUSSION

To our knowledge this is the first study to report longitudinal changes in pulse wave analyses using the Arteriograph® device exclusively in women with chronic hypertension in pregnancy. We demonstrated that longitudinally elevated brachial systolic and diastolic blood pressure predate the development of adverse pregnancy outcome (including SGA10) in women with chronic hypertension. These findings are in keeping with data from other studies demonstrating an association between clinically measured elevated blood pressure and adverse outcome, particularly for those with severe hypertension.(28) An increase in other vascular function parameters across gestation also pre-dates the development of SPE and SGA10 in this cohort. An association between increased central aortic pressure and subsequent diagnosis of pre-eclampsia has previously been demonstrated by Khalil and colleagues (2014) using this device in women who were normotensive at study enrolment.(29) Additionally, raised AIX and AIX-75 have been demonstrated in women with pre-eclampsia, both prior to and at the time of diagnosis.(29-33) Our study did not demonstrate an

association between unadjusted AIX and pregnancy outcome, but AIX-75 was increased across gestation in women who developed SPE, compared to those who did not.

In a population screening study examining the utility of arterial stiffness assessment in predicting adverse pregnancy outcome (including 7500 women), 68 women had chronic hypertension including 21 who subsequently developed SPE and 47 who did not.(33) In those who developed SPE, compared to those who did not, the central aortic pressure was increased, but there was no significant difference in PWV or AIX-75.(33) A cross-sectional cohort study of 41 pregnant women with chronic hypertension, conducted by Tomimatsu and colleagues (2014), also demonstrated an association between increased AIX-75 and SPE.(12) This study found that increased brachial SBP and central aortic pressure pre-dated the development of SPE with SGA10 at 26 to 32 weeks' gestation compared with women with chronic hypertension who had SPE alone, SGA10 alone, or no SPE/SGA10. The approach of subdividing their cohort reduced the power and may have affected the results. Given that our study was not aimed primarily at prediction, no comparison of SGA10 alone was made.

The relationship between blood pressure and placental insufficiency is complex. There are many studies that demonstrate an increased incidence of fetal growth restriction associated with chronic hypertension in pregnancy, both in association with and independently of a diagnosis of SPE.(3-6) Previously fetal growth restriction has been linked to antihypertensive treatment in women with hypertensive disorders of pregnancy, with a hypothesis that the reduction in blood pressure caused by the antihypertensive agents also reduced placental blood flow, leading to fetal growth restriction.(34) However, the Control of Hypertension In Pregnancy Study (CHIPS, reported 2015) demonstrated that there was no significant adverse effect of tight blood pressure control (target DBP 80-85 mmHg), compared to less tight control (target DBP 100-105 mmHg), on the risk of SGA10 between intervention groups (16% versus

20%; odds ratio 0.78, 95% confidence interval 0.56 to 1.08).(35) The impact of antihypertensive treatment on the incidence of fetal growth restriction if a diastolic blood pressure target below 85 mmHg is utilised needs to be established, as the CHIPS protocol recommended cessation of antihypertensive treatment if diastolic was <80 mmHg. However, our study demonstrates an association between increased brachial SBP and DBP across gestation and subsequent delivery of an SGA10 infant in women with chronic hypertension in pregnancy. Though superimposed pre-eclampsia may explain some of this increased risk, the potential contribution of second trimester blood pressure to predict SGA10 warrants further investigation and could aid risk stratification of antenatal care pathways including increased ultrasound surveillance.

No ethnic variation in vascular function parameters was demonstrated in this study. Khalil and colleagues (2009) also found no ethnic variation in vascular function parameters, but in normotensive pregnancy.(36) However, a study by Brewster and colleagues (2010) demonstrated increased resistance artery contractility in Black normotensive pregnant women, compared with White.(37) In order to confirm if ethnic variation in vascular function parameters exist and have a role in the pathophysiology underpinning the ethnic disparity in pregnancy outcome observed in previous cohort studies, a much larger study is needed.

The strengths of this study include recruitment of women with chronic hypertension alone to allow investigation of vascular function differences in this group. The study was conducted at three centres, making the results more generalisable and including a wider UK cohort. Performing longitudinal pulse wave analyses allowed assessment of changes in vascular function parameters that occurred prior to clinical diagnosis of any adverse outcome. The limitations include the relatively small number of participants, though our study was larger than previous cross-sectional studies that examined vascular function in chronic hypertension

alone.(12) The potential clinical utility of these parameters in diagnosis of SPE could not be ascertained as no 'time of disease' readings were obtained, and 8.4% of readings did not record the AIX or PWV, suggesting further optimisation of this technique is required prior to establishing the use of this device in clinical practice.

Future research needs to establish whether the measurement of vascular function parameters (PWV, AIX CAP) in pregnancy complicated by chronic hypertension offers benefit above the standard brachial blood pressure measurements used in current clinical practice. This is particularly pertinent given the association demonstrated within this study between increased clinical systolic and diastolic blood pressure and subsequent SPE and/or SGA10. Differing antihypertensive agent effects on vascular function parameters have been observed, in the absence of brachial blood pressure variation.(38) If such treatment differences were observed in a pregnant population, the assessment of vascular function may prove a useful adjunct to current clinical management of chronic hypertension in pregnancy. It would also be beneficial to establish if vascular function parameters measured in the first or second trimester could be used to predict SPE or SGA10.

In conclusion, there are persistent differences in vascular function parameters and brachial blood pressure through pregnancy in women with chronic hypertension who later develop adverse maternal and perinatal outcome. Further investigation of the possible clinical use of these findings is warranted.

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ETHICAL APPROVAL

The protocol and other study literature was approved by the UK Research Ethics Committee (REC number 13/EE/0390).

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DISCLOSURES

Professor Nelson-Piercy reports personal fees from Alliance Pharmaceuticals, UCB Pharmaceuticals, LEO Pharmaceuticals, Sanofi Aventis and Warner Chilcott outside the submitted work. Professor Cruickshank is current President of the Artery Society which has had donations from Servier Pharmaceuticals. The other investigators have no disclosures to report.

FIGURE CAPTIONS:

Figure 1 Overview flow of study participants including grouping for analyses A, B and C

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SGA10=neonates with birthweight below the 10th centile

Participants of vascular function sub-study only presented in this schematic. The five second trimester losses included one fetal demise at 15 weeks' gestation, one miscarriage secondary to premature rupture of membranes and subsequent induction for chorioamnionitis, one late miscarriage secondary to cervical incompetence, and two terminations for fetal indications.

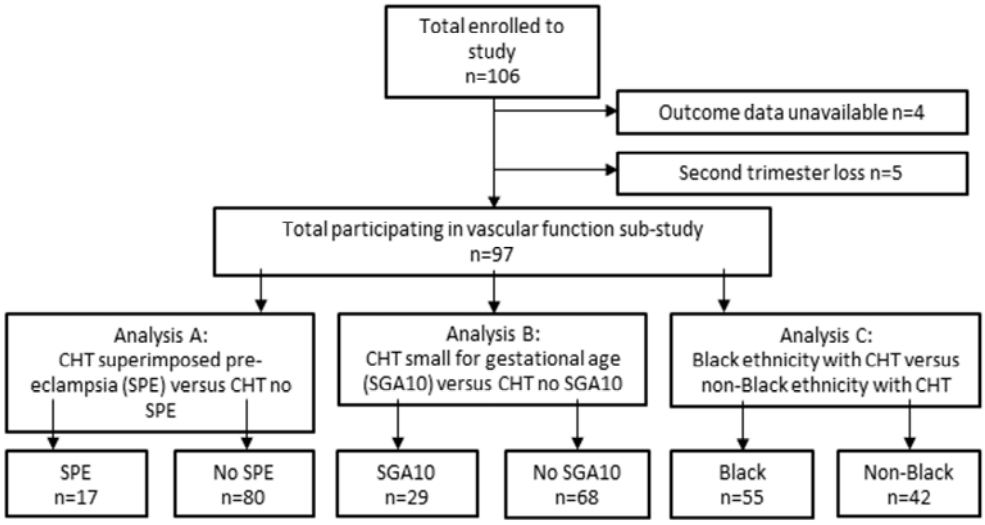
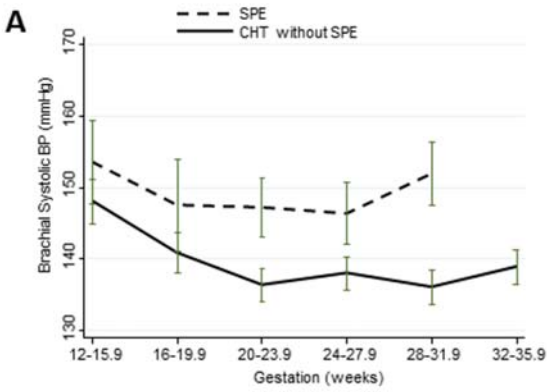
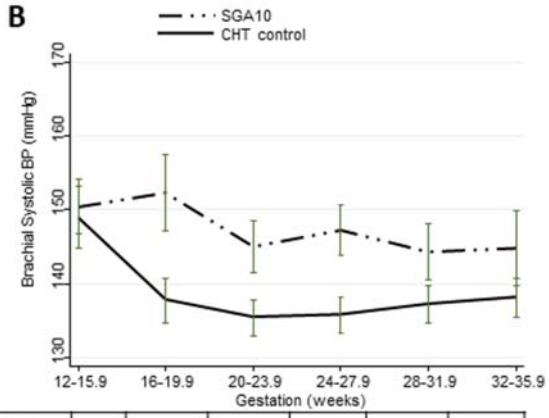


Figure 2 Brachial systolic blood pressure across gestation in pregnant women with chronic hypertension.

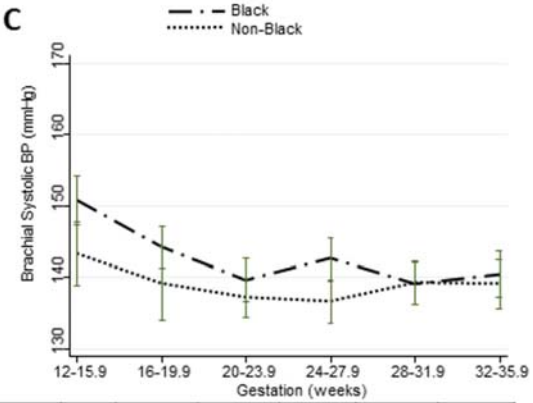
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	14	13	12	
CHT control	22	26	42	42	39	37



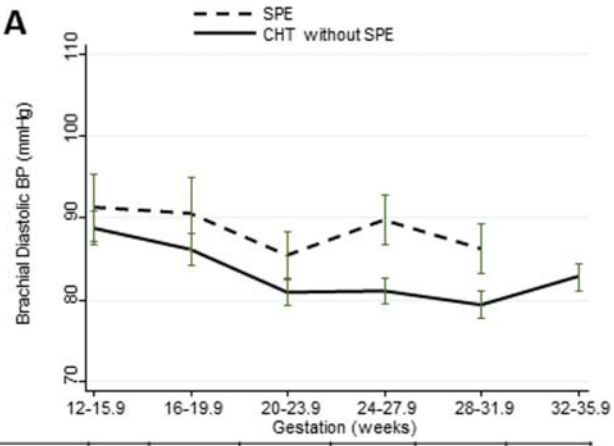
Number of readings						
SGA10	16	8	18	19	15	8
CHT control	12	23	38	36	36	31



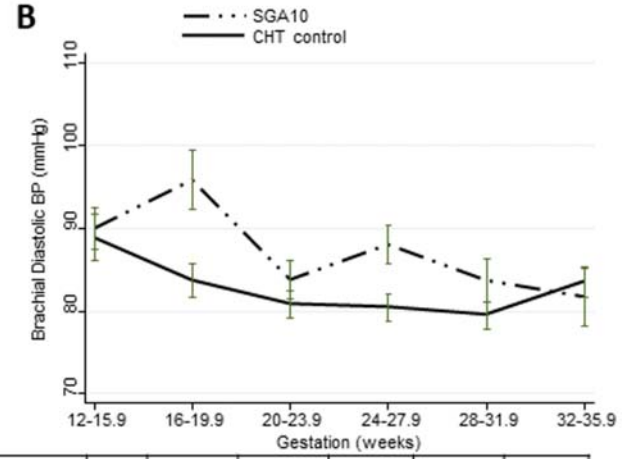
Number of readings						
Black	19	25	25	27	26	21
Non Black	11	8	31	28	25	18

Figure 3 Brachial diastolic blood pressure across gestation in pregnant women with chronic hypertension.

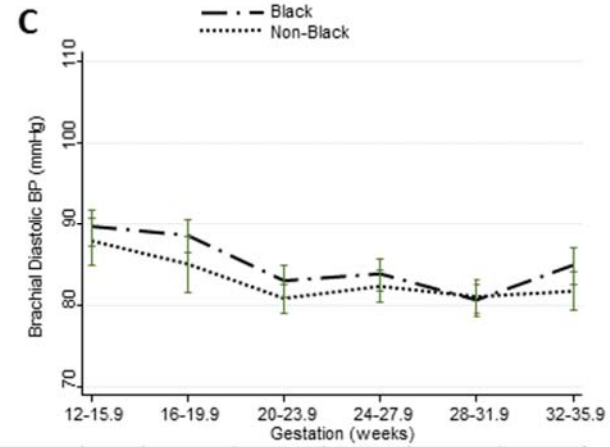
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	14	13	12	
CHT control	22	26	42	42	39	37



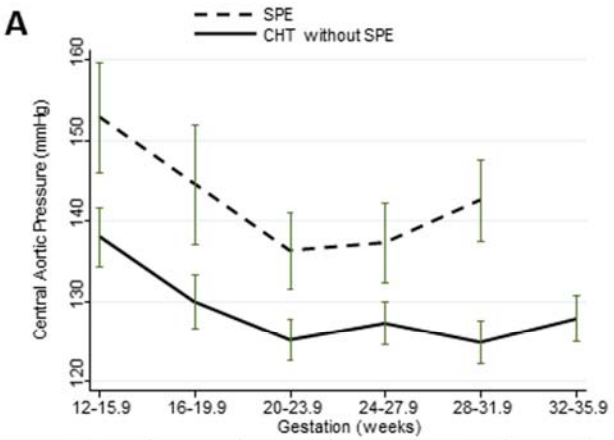
Number of readings						
SGA10	16	8	18	19	15	8
CHT control	12	23	38	36	36	31



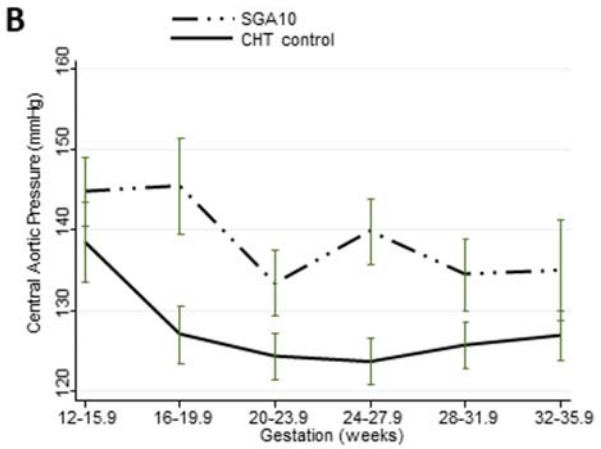
Number of readings						
Black	19	25	25	27	26	21
Non Black	11	8	31	28	25	18

Figure 4 Central aortic blood pressure across gestation in pregnant women with chronic hypertension

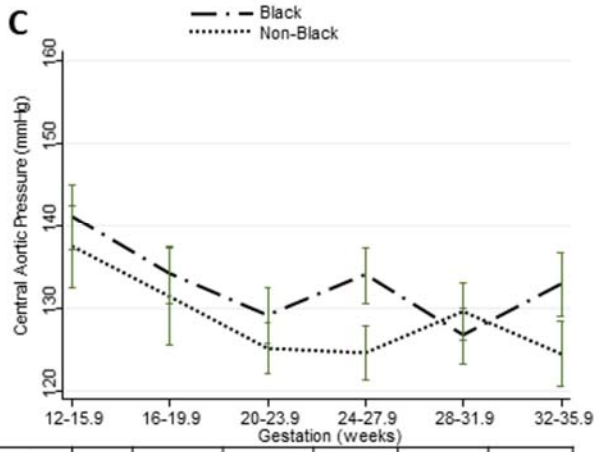
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	14	13	12	
CHT control	22	26	42	42	39	37



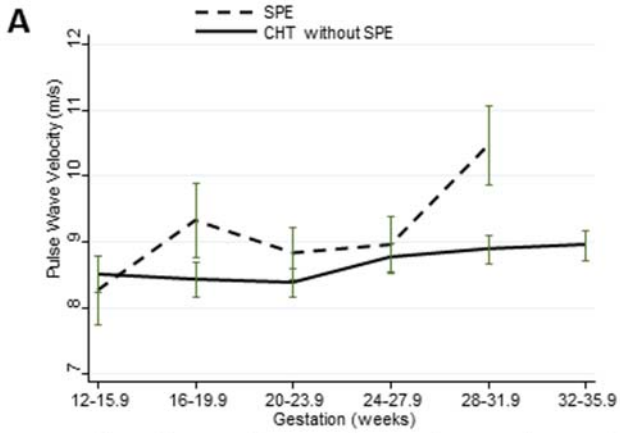
Number of readings						
SGA10	16	8	18	19	15	8
CHT control	12	23	38	36	36	31



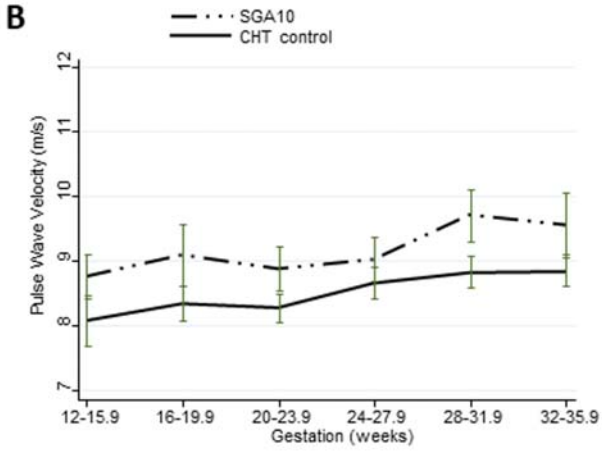
Number of readings						
Black	19	25	25	27	26	21
Non Black	11	8	31	28	25	18

Figure 5 Pulse wave velocity across gestation in pregnant women with chronic hypertension

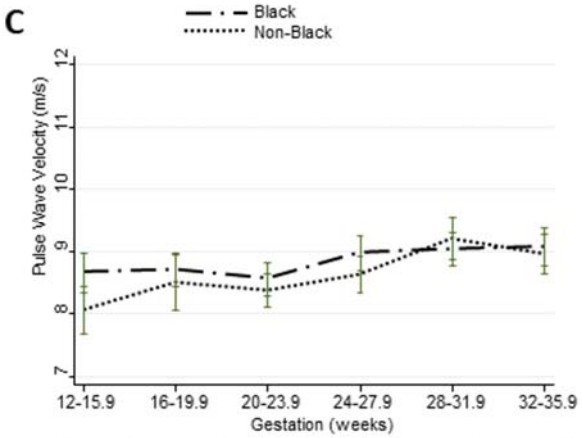
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	13	11	5	
CHT control	20	25	41	36	38	34



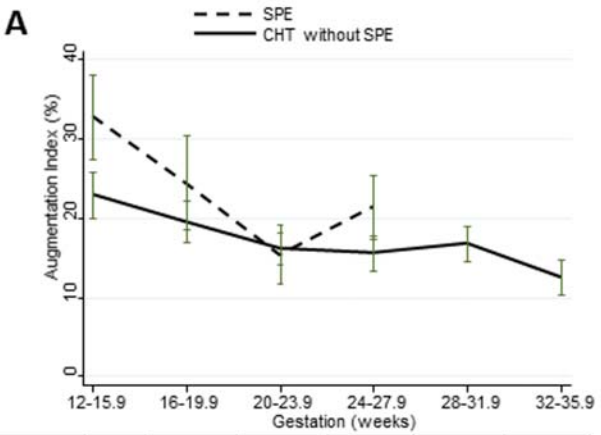
Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	32	30



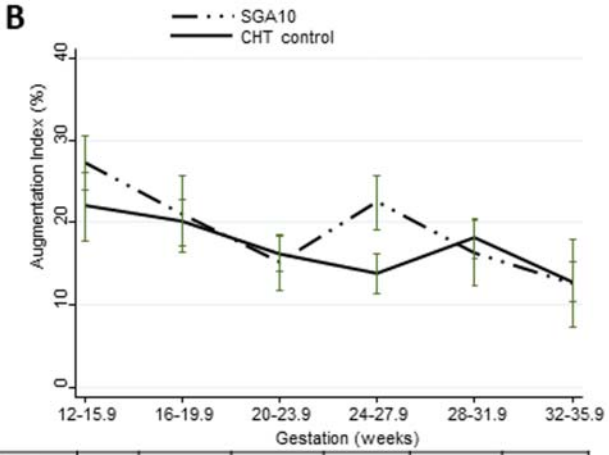
Number of readings						
Black	17	24	24	22	27	18
Non Black	11	8	30	25	16	18

Figure 6 Augmentation index across gestation in pregnant women with chronic hypertension

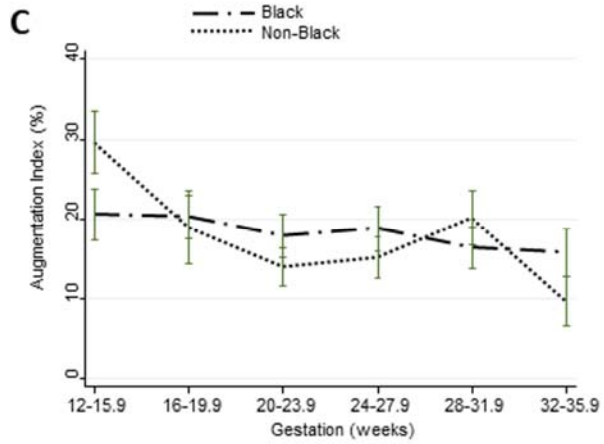
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	13	11		
CHT control	20	25	41	36	38	34



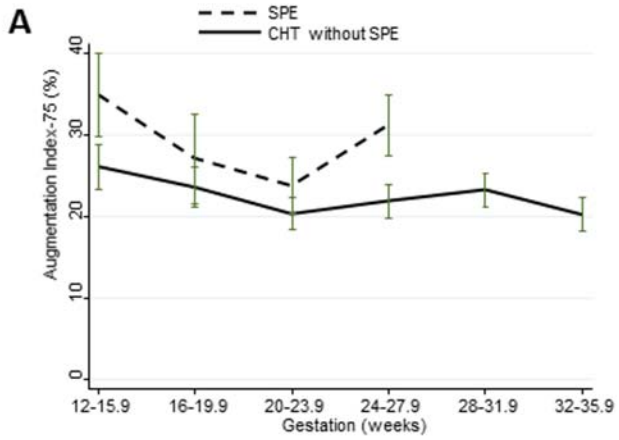
Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	31	30



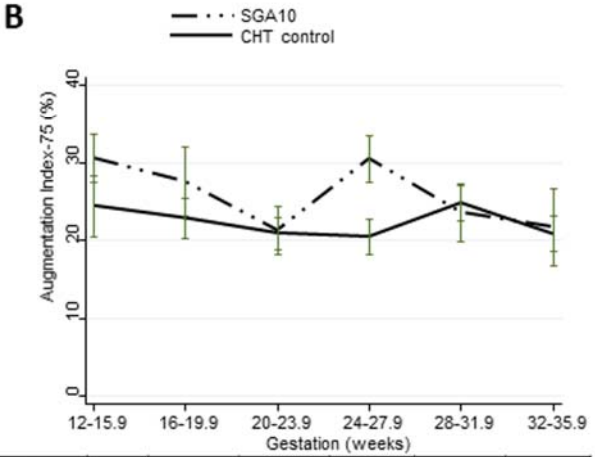
Number of readings						
Black	17	24	24	22	26	18
Non Black	11	8	30	25	16	18

Figure 7 Augmentation index adjusted to a heart rate of 75 beats per minute across gestation in pregnant women with chronic hypertension

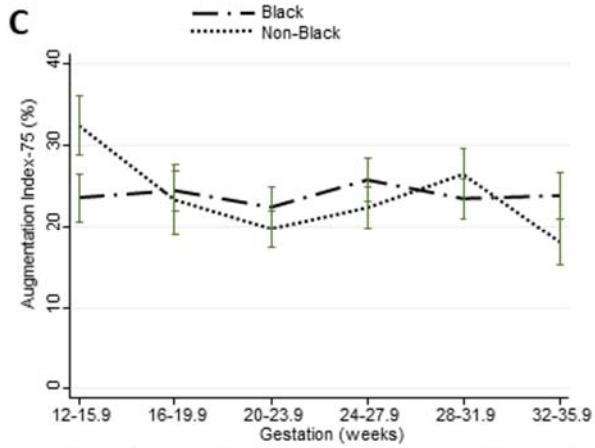
Comparison A: SPE vs no SPE. Comparison B: SGA10 vs no SGA10. Comparison C: women of Black ethnicity vs women of non-Black ethnicity. The limits of the axes represent the maximum and minimum value within the dataset for each parameter.



Number of readings						
SPE	6	5	13	11		
CHT control	20	25	41	36	37	34



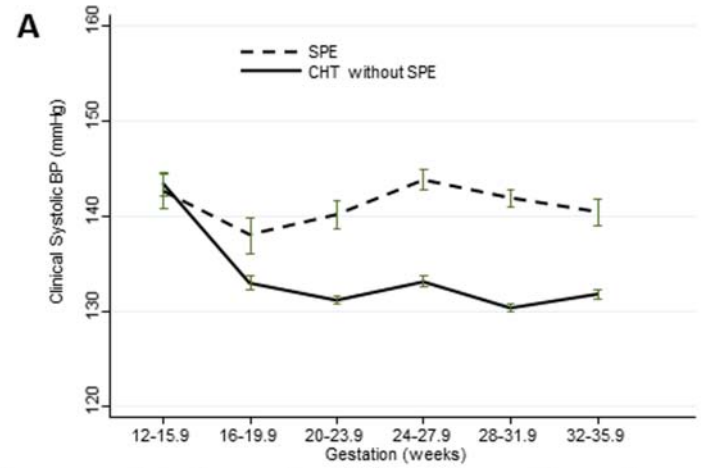
Number of readings						
SGA10	16	8	16	17	11	6
CHT control	10	22	38	30	30	30



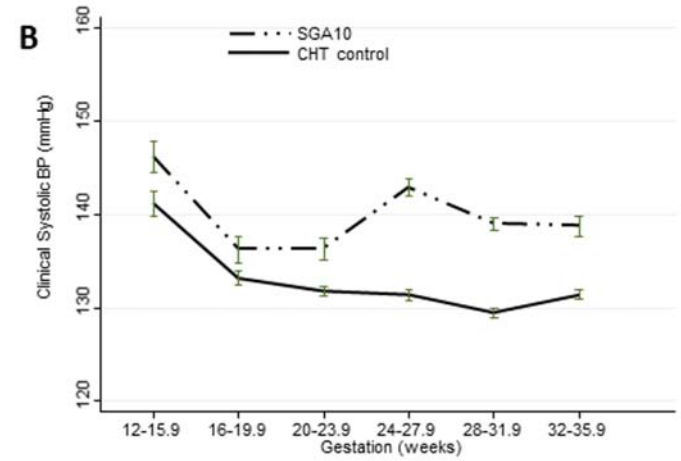
Number of readings						
Black	17	24	24	22	25	18
Non Black	11	8	30	25	16	18

Figure 8 Clinical systolic blood pressure across gestation in pregnant women with chronic hypertension.

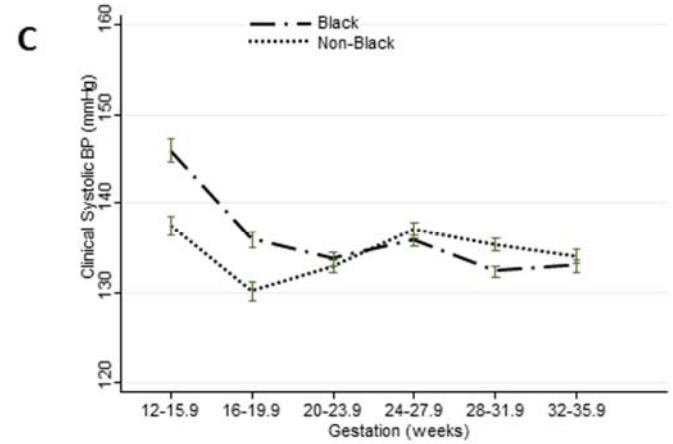
Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: Women giving birth to infants <10th birthweight centile. Comparison C: women of Black ethnicity versus non-Black ethnicity.



Number of readings						
SPE	42	87	133	230	240	153
CHT control	191	305	427	535	606	699



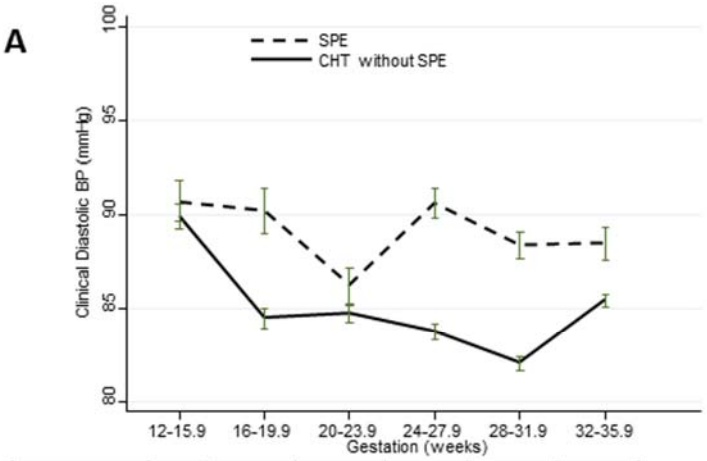
Number of readings						
SGA10	99	121	191	330	371	232
CHT control	134	271	369	435	475	620



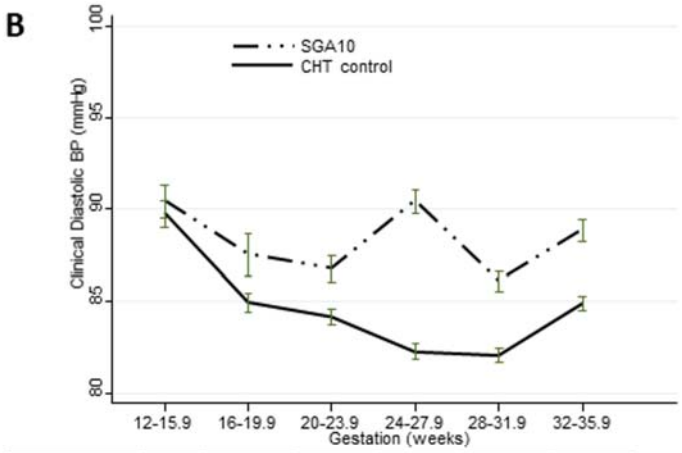
Number of readings						
Black	159	269	316	420	465	489
Non Black	74	123	244	345	381	363

Figure 9 Clinical diastolic blood pressure across gestation in pregnant women with chronic hypertension.

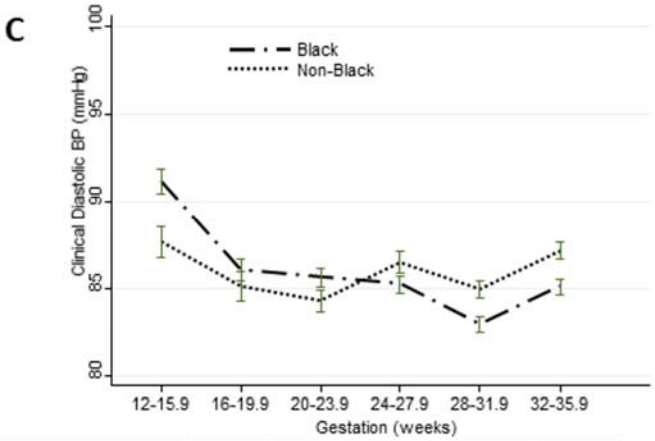
Comparison A: superimposed pre-eclampsia (SPE) versus no SPE. Comparison B: Women giving birth to infants <10th birthweight centile. Comparison C: women of Black ethnicity versus non-Black ethnicity.



Number of readings						
SPE	42	87	133	230	240	153
CHT control	191	305	427	535	606	699



Number of readings						
SGA10	99	121	191	330	371	232
CHT control	134	271	369	435	475	620



Number of readings						
Black	159	269	316	420	465	489
Non Black	74	123	244	345	381	363

TABLES:

Table 1 Baseline demographics for the cohort

Characteristic	All CHT n=97	SPE n=17	CHT no SPE n=80	Black ethnicity n=55	Non-Black ethnicity n=42
Maternal age at study entry, years mean (SD)	35 (6)	34 (6)	35 (5)	35 (5)	35 (6)
Body mass index, Kg/m^2 mean (SD)	31 (5.7)	31 (4.6)	30 (6.0)	32* (5.6)	29 (6.5)
Nulliparity number (%)	15 (15%)	4 (24%)	11 (14%)	2* (3.6%)	13 (31%)
Smoker number (%)	1 (1.0%)	0	1 (1.3%)	0 (0%)	1 (2.4%)
Booking blood pressure, mmHg median (IQR)					
Systolic	136 (126 to 142)	138 (130 to 142)	136 (125 to 143)	140* (128 to 148)	134 (125 to 140)
Diastolic	88 (80 to 92)	84 (80 to 89)	88 (80 to 92)	88 (80 to 92)	84 (80 to 90)
Centre number (%)					
Guy's and St Thomas' NHS Foundation Trust	54 (56%)	6 (35%)	48 (60%)	35 (64%)	19 (45%)

Central Manchester University Hospitals NHS Foundation Trust	32 (33%)	9 (53%)	23 (29%)	14 (25%)	18 (43%)
St George's University Hospitals NHS Foundation Trust	11 (11%)	2 (12%)	9 (11%)	6 (11%)	5 (12%)
Randomised to antihypertensive treatment number (%)	87 (90%)	16 (94%)	71 (89%)	50 (91%)	37 (88%)
Labetalol	45 (47%)	6 (35%)	39 (49%)	26 (47%)	19 (45%)
Nifedipine	42 (43%)	10 (59%)	32 (40%)	24 (44%)	18 (43%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, SD= standard deviation, IQR= interquartile range

**denotes characteristics that are significantly different between the compared subgroups (p=<0.05)*

Table 2 Maternal outcomes of the cohort

Outcome	All CHT n=97	SPE n=17	CHT no SPE n=80	Black ethnicity n=55	Non-Black ethnicity n=42
Highest blood pressure per woman, mmHg median (IQR)					
Systolic	162 (151 to 174)	180* (166 to 189)	160 (150 to 169)	167 (153 to 175)	158 (150 to 171)
Diastolic	98 (91 to 106)	107* (98 to 116)	97 (90 to 103)	100 (92 to 107)	96 (90 to 104)
Superimposed pre-eclampsia number (%)	17 (18%)	17 (100%)	0 (0%)	7 (13%)	10 (24%)
Mode of delivery number (%)					
Spontaneous vaginal delivery	31 (32%)	2 (12%)	29 (36%)	16 (29%)	15 (36%)
Assisted vaginal delivery	5 (5.2%)	2 (12%)	3 (3.8%)	4 (7.3%)	1 (2.4%)
Elective Caesarean section	17 (18%)	0 (0%)	17 (21%)	9 (16%)	8 (19%)
Emergency Caesarean section	44 (45%)	13* (76%)	31 (39%)	26 (47%)	18 (43%)
Gestation at delivery, weeks median (IQR)	38 (37 to 39.3)	33* (30.3 to 36.4)	39 (37.8 to 39.3)	38 (37.2 to 39.3)	38 (36.4 to 39.2)
Pre-term birth <37 weeks	23 (24%)	13* (76%)	10 (13%)	11 (20%)	12 (29%)

number (%)					
Perinatal outcome number (%)					
Livebirth	94 (97%)	17 (100%)	77 (96%)	54 (98%)	40 (95%)
Stillbirth	3 (3.1%)	0 (0%)	3 (3.8%)	1 (1.8%)	2 (4.8%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, IQR= interquartile range

**denotes outcomes that are significantly different between the compared groups*

***Severe hypertension= systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg*

Table 3 Neonatal outcomes for the live births within the cohort

Outcome	All CHT n=94	SPE n=17	CHT no SPE n=77	Black ethnicity n=54	Non-Black ethnicity n=40
Birthweight, g Median (IQR)	2940 (2580 to 3260)	1560* (1040 to 2510)	3030 (2790 to 3460)	2980 (2520 to 3190)	2930 (2650 to 3530)
Birthweight <10th centile (SGA10) number (%)	29 (30%)	12* (71%)	17 (22%)	18 (33%)	11 (28%)
Birthweight <3rd centile number (%)	14 (14%)	10* (59%)	4 (5.2%)	9 (17%)	5 (13%)
Neonatal unit admission number (%)	21 (22%)	13* (76%)	8 (10%)	10 (19%)	11 (28%)

CHT= chronic hypertension, SPE=superimposed pre-eclampsia, IQR= interquartile range

**denotes outcomes that are significantly different between the compared groups*

Table 4 Mean vascular function parameters and adjusted mean differences across gestation in women who did and did not develop superimposed pre-eclampsia

Parameter	SPE n=17 mean (SD)	CHT no SPE n=80 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	148 (17)	139 (15)	10 (4 to 16)	0.002
Brachial DBP (mmHg)	87 (10)	82 (10)	5 (1 to 9)	0.01
CAP (mmHg)	139 (22)	128 (16)	12 (5 to 20)	0.001
PWV (m/s)	9.0 (1.7)	8.6 (1.4)	0.6 (-0.2 to 1.3)	0.12
AIX (%)	21 (16)	17 (13)	4 (-1 to 9)	0.11
AIX-75 (%)	29 (13)	22 (12)	6 (1 to 11)	0.01

Mean difference adjusted for gestation. SD= standard deviation, SPE= superimposed pre-eclampsia, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute

Table 5 Mean vascular function parameters across and adjusted mean differences gestation in women who gave birth to a small for gestational age infant (<10th birthweight centile)

Parameter	SGA10 n=29 mean (SD)	CHT no SGA10 n=68 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	146 (18)	138 (13)	9 (4 to 14)	0.001
Brachial DBP (mmHg)	86 (13)	82 (9)	4 (1 to 8)	0.01
CAP (mmHg)	137 (22)	127 (15)	11 (5 to 18)	<0.0001
PWV (m/s)	9.1 (1.7)	8.5 (1.3)	0.7 (0.1 to 1.4)	0.02
AIX (%)	19 (15)	17 (13)	3 (-2 to 7)	0.25
AIX-75 (%)	26 (13)	22 (12)	4 (0 to 8)	0.05

Mean difference adjusted for gestation. SD= standard deviation, SGA10= birthweight <10th centile, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute

Table 6 Mean vascular function parameters and adjusted mean differences across gestation in women of Black and non-Black ethnicity

Parameter	Black n=55 mean (SD)	Non-Black n=42 mean (SD)	Adjusted mean difference (95% confidence interval)	Significance (P value)
Brachial SBP (mmHg)	142 (17)	139 (13)	4 (-1 to 8)	0.17
Brachial DBP (mmHg)	84 (11)	82 (9)	2 (-1 to 5)	0.18
CAP (mmHg)	132 (19)	128 (17)	5 (-1 to 11)	0.12
PWV (m/s)	8.7 (1.5)	8.6 (1.5)	0.3 (-0.3 to 0.9)	0.34
AIX (%)	18 (13)	17 (15)	2 (-2 to 6)	0.45
AIX-75 (%)	23 (12)	23 (14)	1 (-3 to 5)	0.52

Mean difference adjusted for gestation. SD= standard deviation, CHT= chronic hypertensive, SBP= systolic blood pressure, DBP= diastolic blood pressure, CAP= central aortic pressure, PWV= pulse wave velocity, AIX= augmentation index, AIX-75= augmentation index adjusted for a heart rate of 75 beats per minute